PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Applicant's or agent's file reference see form PCT/ISA/220	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet) **FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003273	24.09.2004	01.10.2003

International Patent Classification (IPC) or both national classification and IPC
A61K35/74, A61K31/19, A61K31/205, A61P29/00

Applicant
DANISCO A/S

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IB2004/003273

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-8, 11-13, 17-25, 29-30 and 34 (in part), 16, 28, 33 and 35-39 (complete) and 17-19 and 21-27 (with respect to industrial applicability)

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-8, 11-13, 17-25, 29-30 and 34 (in part), 16, 28, 33 and 35-39 (complete) and 17-19 and 21-27 (with respect to industrial applicability)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-15, 17-27, 29-32 and 34 (in part)

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10,15,27,32
	No:	Claims	1-9, 11-14, 17-26, 29-31 and 34
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-15, 17-27, 29-32 and 34
Industrial applicability (IA)	Yes:	Claims	1-15, 20, 29-32 and 34
	No:	Claims	-

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Present **claims 1-8, 11-13, 17-25, 29-30 and 34** relate to microorganisms which are defined by reference to a desirable characteristic or property, namely, that they are able to increase the amount of COX-1 mRNA in the cell and/or decrease the amount of COX-2 mRNA. The claims cover all microorganisms having this characteristic or property, whereas the application provides support within the meaning of Art. 6 PCT and disclosure within the meaning of Art. 5 PCT for only a very limited number of such microorganisms. Thus, said claims are not supported and disclosed over their whole breadth (see PCT International Search and preliminary Examination Guidelines, 5.43). Independent of the above reasoning, the claims also lack clarity (Art. 6 PCT). An attempt is made to define the microorganisms by reference to the result to be achieved. Article 6 in conjunction with Rule 6.3 (a) PCT requires that all essential technical features of the claimed invention have to be indicated in the claim in technical terms. Claims which attempt to define the invention by a result to be achieved, should not be allowed, in particular if they only amount to claiming the underlying technical problem (see PCT International Search and preliminary Examination Guidelines, 5.35). Therefore, the claims need to be restricted to those microorganisms which are supported and disclosed in the application, i.e. bacteria of the genus *Bifidobacterium*.

Claims 17-19 and 21-27 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The application lacks unity of inventions as required by Article 3(4)(iii) and 17(3)(a) PCT for the following reasons:

The inventions as defined above relate to various pharmaceutical agents. The common concept underlying the present application is that those pharmaceutical agents have anti-inflammatory activity and can be used together with non-steroidal anti-inflammatory agent (NSAIDs). However, anti-inflammatory pharmaceutical agents suitable for use with NSAIDs are known in the art. For instance, WO03010297 describes the use of Bifidobacterium strains which are suitable for the treatment of inflammatory diseases of the bowel and which can be administered with NSAIDs (see page 8, lines 20-26 and pages 30-31, in particular lines 21-24 on page 31).

In light of this prior art, the above mentioned common concept is not novel and the problem underlying the present application can be redefined as the provision of further anti-inflammatory pharmaceutical agents. Thus, the following solutions to the above problem can be identified:

Invention 1 (claims 1-15, 17-27, 29-32 and 34, in part): Use of a microorganism for the manufacture of a medicament for use in increasing the amount of COX-1 mRNA in a cell and for the treatment of inflammatory and cancer diseases, or to prevent side-effects associated with NSAIDs, pharmaceutical preparations comprising a microorganism and NSAID, methods for treatment of inflammatory and cancer diseases or for preventing side effects associated with NSAID administration using said microorganism, pharmaceutical packs comprising a microorganism and a NSAID.

Invention 2 (claims 1-15, 17-27, 29-32 and 34, in part): As invention 1 but wherein the pharmaceutical agent is acetate (a microorganism metabolite).

Invention 3 (claims 1-15, 17-27, 29-32 and 34, in part): As invention 1 but wherein the pharmaceutical agent is lactate (a microorganism metabolite).

Invention 4 (claims 16, 28, 33 and 35-39): As invention 1 but wherein the pharmaceutical agent is a combination of microorganism and/or metabolite thereof and betaine.

Due to the fact that anti-inflammatory reagents are known in the art and due to the fact that no other technical feature can be distinguished which, in the light of the prior art, could be regarded as a special technical feature in the sense of Rule 13.2 PCT due to the essential

differences in the primary structures of the claimed agents, there is no single general inventive concept underlying the plurality of claimed inventions of the present application in the sense of Rule 13.1 PCT.

Consequently, the application lacks unity of invention and the different inventions are as formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT. It should be noted that for regrouping the different inventions, the ISA has taken into account the balance between necessary search efforts and the levying of additional fees.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document/s/:

D1: WO 03/010297 A (ALIMENTARY HEALTH LIMITED; COLLINS, JOHN, KEVIN; O'SULLIVAN, GERALD, C) 6 February 2003 (2003-02-06)

D2: UEJIMA M ET AL: "ROLE OF INTESTINAL BACTERIA IN ILLEAL ULCER FORMATION IN RATS TREATED WITH A NONSTEROIDAL ANTIINFLAMMATORY DRUG" MICROBIOLOGY AND IMMUNOLOGY, TOKYO, JP, vol. 40, no. 8, 1996, pages 553-560, XP008008800 ISSN: 0385-5600

D3: US-A-5 922 375 (LUCHANSKY ET AL) 13 July 1999 (1999-07-13)

D1 describes *Bifidobacterium* strains isolated from human gastrointestinal tract and their use for the preparation of anti-inflammatory therapeutic agents, in particular, for the treatment of inflammatory bowel disease (see page 5, lines 11-13, pages 30, line 1 to page 31, line 24). The document also suggests the use of the *Bifidobacterium* strains for the treatment and/or prevention of cancer (see page 31, line 26 to page 32, line 17). D1 also suggests the possibility of combining the *Bifidobacterium* strains with a non-steroidal anti-inflammatory agent (NSAIDs) (see page 31, lines 21-24). This document anticipates the subject-matter of claims relating to the use of *Bifidobacterium* strains as such or in combination with NSIADs for the treatment of inflammatory diseases, either if drafted as second medical use, as first medical uses or as pharmaceutical preparations (**claims 4, 8, 9, 11-14, 17-19, 21, 23-26, 29-31 and 34**). Furthermore, even if D1 is silent about the

effect of the *Bifidobacterium* strains on COX-1 and COX-2 activity, the mechanism of action which underlies a given medical use is implicit to said use, so that the disclosure in D1 of the medical use of *Bifidobacterium* strains for the treatment of inflammatory diseases takes away the novelty of the claims which relate to said medical use when defined by the mechanism of action (**claims 1-3, 7**).

D2 discloses the therapeutic effects of *Bifidobacterium* adolescentis on ileal ulcer formation in patients showing ileal ulcer as a consequence of treatment with BFMeT (an NSAID) (see page 556, left-hand column, second last paragraph to page 558, left-hand column, first paragraph and Table 4). Thus, this document clearly anticipates the idea of using microorganisms of the genus *Bifidobacterium* for increasing the tolerance of a subject to anti-inflammatory drugs or to prevent and treat side-effects associated with anti-inflammatory disease. Thus, the subject-matter of **claims 5-9 and 22-26** lacks novelty. Furthermore, the disclosure in D2 that microorganisms of the strain *Bifidobacterium adolescentis* are able to reduce ileal ulcer when administered prior to the agent inducing the ulcer would provide a clear hint to the skilled person to combine both the damaging agent and the remedy within the same composition, thus arriving to the subject-matter of claims relating to compositions comprising *Bifidobacterium* cells and an NSAID (**claims 29-31 and 34**).

Claims 10, 15, 27, 32 define the specific *Bifidobacterium* strains which are employed in the medical uses of the corresponding independent claims. These strains have not been anticipated in the prior art and therefore, are new. However, due to the fact that the general use of *Bifidobacterium* strains is known from the prior art, the specific *Bifidobacterium* strains recited in the claims are selections which can only be considered as involving an inventive step if they provide some unexpected or surprising result when compared with the strains disclosed in D1 and D2.

D3 teaches the use of a microorganism of the genus *Bifidobacterium* as a food additive, with the purpose of increasing body weight in livestock (piglets) (see column 1, line 65 to column 2, line 45, column 5, lines 2-5 and references on column 1, lines 39-44). Thus, the method of **claim 20** which relates to the use of microorganisms of the genus *Bifidobacterium* for the treatment of reduced wight gain in livestock is not new.

In conclusion, it appears that the only contribution of the present application would be the discovery that cells of the genus *Bifidobacterium* are able to modulate the expression of COX-1 and COX-2. This effect appears to underlie the known therapeutic effects of *Bifidobacterium* cells but can not serve to restore novelty on said methods since they have been described in the art. It appears therefore that the only part of the application which can result in an allowable claim would be an in vitro method for increasing the amount of COX-1 mRNA and/or to decrease the amount of COX-2 mRNA.

Re Item VIII

Certain observations on the international application

Claims 1-3 attempt to define a medical use of microorganisms of the genus *Bifidobacterium* on the basis of their mechanism of action (increasing the amount of COX-1 mRNA in the cell and/or decreasing the amount of COX-2 mRNA in the cell). This definition lacks clarity since medical uses need to be referred to a specific and not to the underlying mechanisms of action. Alternatively, claims 1-3 could be reworded as the in vitro use of microorganisms for modulating cycloxygenase activities in the cell.

Claims 4 and 19 list a whole list of diseases which can be treated with the microorganisms of the application. However, the application provides support and disclosure only for those diseases which are associated which respond to compounds of the NSAID family, i.e. inflammatory diseases and colon cancer (first paragraph on page 3 of the description). Thus, the claim can only be accepted if restricted to those diseases which are clearly supported, disclosed and for which there exists experimental evidence suggesting that are associated to an increased COX-2 activity. Furthermore, not all the conditions listed on the claims can be considered as diseases (i.e. aging, fatigue).